CUTANEOUS MANIFESTATIONS OF INTERNAL DISEASE

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DISCLOSURES

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Objectives

- Identify three common cutaneous disorders with possible internal manifestations
- List two common cutaneous presentations of diabetes
- Describe two systemic symptoms of Wegener's Granulomatosis
Psoriasis

- Papulosquamous eruption
- Well-circumscribed erythematous macular and papular lesions with loosely adherent silvery white scale
- Remissions and spontaneous recurrences
- Both genetic and environmental factors predispose development
- Unpredictable course
- Great social, psychological, & economic stress
Pathophysiology

- Epidermis thickened; silver-white scale

- Transit time from basal cell layer to surface of skin is 3-4 days, compared to normal cell transit time of 20-28 days

- Dermis highly vascular

- Pinpoint sites of bleeding when scale removed (Auspitz sign)

- Cutaneous trauma causes isomorphic response (Koebner phenomenon)

- Itching is variable
Pathophysiology

- **T-cell mediated disorder**
- **Over-active inflammatory response**
- **Tumor necrosis factor-α (TNF-α): pro-inflammatory cytokine**
- **TNF α levels elevated in the skin and synovium of patients with psoriasis**
Epidemiology

- 1-3% of the population
- 25-45% after age ten
- 2:1 ratio of females to males in children
- Both sexes affected equally in adults
- Familial tendency
Psoriasis Comorbidities

- Psoriatic Arthritis
- Crohn’s Disease, Ulcerative colitis
- Depression
- Cardiovascular disease
- Obesity
- Diabetes
- Hypertension
Psoriasis Treatment Options

- **Light therapy**
  - Ultraviolet B (UVB)
  - Ultraviolet A (UVA)
  - PUVA (psoralens with UVA)
  - Home UVB

- **Adjunct therapies**
  - Topical Steroids
  - Vitamin A and D derivatives
  - Topical calcineurin inhibitors
  - Intralesional steroid injections
  - Coal Tar (Scytera®)

- **Systemic drugs**
  - Acitretin (Soriatane®)
  - Methotrexate (MTX)
  - Cyclosporine (CsA)
  - Otezla (Apremilast)

- **Biologic therapy**
  - Alefacept (Amevive®)
  - Etanercept (Enbrel®)
  - Adalimumab (Humira®)
  - Infliximab (Remicade®)
  - Ustekinumab (Stelara®)
  - Cizia (certolizumab pegol)
  - Cosentyx (Secukinumab)
  - Taltz (Ixekizumab)
Malignant Skin Tumors

- **Cutaneous T-cell Lymphomas (CTCL)**
  - Primary site of malignant T-lymphocyte proliferation
  - Type of non-Hodgkin lymphoma
  - Malignant CD4+ T cells (lymphocytes) invade lymphatic nodes, blood, and visceral organs
    - Mycosis Fungoides (MF)
    - Sèzary Syndrome (SS)
CTCL Epidemiology

- Incidence tripled from 1973-2002
- 32% more common in blacks
- Male-female ratio 2:1
- Increased incidence with age
- Confirmed but uncommon in children
- 3.9% of all non-Hodgkin lymphomas
  - MF 72% of CTCL cases; SS 2.5%
CTCL Incidence

- Increased incidence in areas with
  - High provider density
  - High family income
  - Higher education
  - High home property values
  - ??access to medical care
  - ??earlier and better diagnosis
CTCL Pathophysiology

- **Cause unknown**
  - **Infectious agents proposed:** bacteria & viruses
    - **Cytomegalovirus**
    - **Epstein-Barr**
    - **Data not strong enough to conclude causal relation**
CTCL Pathophysiology

- Multiple abnormalities in cytokine expression, chemokine expression and antigen presentation
- Malignant CD4+ T cells release cytokines, causing proliferation of keratinocytes
- Causes scaling, thickening of epidermis, and pruritus
- Cytokines, including IL4, contribute to immunosuppression
Mycosis Fungoides (MF)

- Months to years diagnosed with psoriasis, nummular eczema, parapsoriasis

- Stages:
  - Patch: Varying shades of red, scaling and non-scaling
  - Plaque: Round, oval or bizarre shapes, randomly distributed, often non-exposed
  - Tumor: Nodules, tumors, with & without ulceration; palmar hyperkeratosis, hair loss
MF Work-up

- Repeated and multiple biopsies
- CBC with smear
- Chest X-ray
- Lymph node biopsy
MF Treatment

- Symptomatic, extent of disease
  - Topical corticosteroids
  - Nitrogen Mustard
  - Carmustine
  - Phototherapy
  - Radiation
Sèzary Syndrome (SS)

- Leukemic form of MF
- Universal erythroderma
- Lymphadenopathy
- Cellular infiltrates of atypical lymphocytes (Sèzary cells) in skin and blood
- Pts. appear sick, shivering, scared, generalized scaling erythroderma and thickening of skin; diffuse hair loss, generalized lymphadenopathy
SS Management

- Same as MF
- Supportive measures for erythroderma
- Without treatment, disease is progressive
  - Patients die from opportunistic infections
Sweet Syndrome

- Acute febrile neutrophilic dermatosis
- Associated with inflammatory bowel diseases
  - Ulcerative colitis
  - Crohn disease
- Autoimmune syndromes
  - Hashimoto thyroiditis
  - Sjörgren syndrome
- Intestinal bypass surgery
Pathophysiology

- Hypersensitivity reaction
  - Infection
  - Tumor antigen, drug
- Lesions in upper dermis
  - Vesicular or bullous appearance
Subtypes

- **Idiopathic**
  - Women 30-60 years of age
  - URI, IBD (Crohn, ulcerative colitis), or pregnancy
  - Patients ill, fever, physical distress

- **Malignancy-associated**
  - Males:females equal
  - Solid tumor of breast, GU, GI systems
  - Leukemia, lymphoma

- **Drug induced**
  - Isotretinoin
  - OCP
  - Trimethoprim/sulfamethoxazole
  - Furosemide
  - Minocycline, doxycycline

- Lesions appear 1 week-1 month after administration and resolve after drug stopped
Clinical Presentation

- Painful, erythematous papules
- May be vesicles or bullae
- Dorsum of hands, face, neck, trunk
- Sudden onset fever, abdominal pain, malaise, joint pain, headache, conjunctivitis, pregnancy
Differential

- Pyoderma gangrenosum
- Bullous disease
- Erythema multiforme
- Bowel-associated dermatosis
- Bechet disease
- Erythema nodosum
- Drug eruption
- Urticaria
- Cellulitis
- Paraneoplastic syndrome
Diagnostics

- Biopsy
- Labs:
  - CBC/Diff: ↑WBC’s, neutrophilia
  - ↑ESR, alkaline phosphatase
Management

- **Systemic steroids**
- **Anti-inflammatory antibiotics** (Tetracycline class)
- **Off-label dapsone**
Dermatomyositis

- Violaceous inflammatory changes of eyelids and periorbital areas (heliotrope)
- Variable edema
- Violaceous flat-topped papules over knuckles (Gottron papule)
- Erythema of face, neck, upper trunk
- Myositis, muscle weakness, dysphagia, burning and pruritus of entire scalp
Dermatomyositis Etiology

- **Cutaneous involvement:** 30-40% of adults; 95% of children
- **Male=Female**
- **Over 50 years higher risk for collagen vascular disease and malignancy:** ovarian, breast, bronchopulmonary, GI
- **Juvenile:** associated with vasculitis and calcinosis
Dermatomyositis Diagnosis

- Serum muscle enzymes, AST, ALT, ANA, urinary creatine
- MRI of muscles: focal lesions
- ECG myocarditis, atrial ventricular irritability, atrioventricular block
- X-ray: Chest ± interstitial fibrosis. Esophagus: reduced peristalsis
- Muscle biopsy: muscle fiber and capillary damage
Dermatomyositis Management

- *Prednisone.* Taper when muscle enzyme levels approach normal. Best combined with azathioprine
- *Alternatives:* MTX, cyclophosphamide, cyclosporine, TNF agents
- *Physical therapy, rest*
Neurofibromatosis

- Autosomal dominant
- NF1: von Recklinghausen
  - Diagnostic sign: Lisch nodules
- NF2: bilateral acoustic neuroma
Differential Diagnosis

- Brown Cafe' Au Lait lesions (CAL)
- McCune-Albright syndrome
- 2 of 3: polyostotic fibrous dysplasia, cafe'au lait pigmentation, autonomous endocrine hyperfunction
- 10-20% of normal population have few CAL macules (<3)
Two of the following criteria:

- Multiple CAL macules: >6 w/1.5cm diameter adults; >5 macules w/0.5cm diameter children <5 years
- Multiple freckles in axillary and inguinal areas
- 2/more neurofibromas of any type or 1 plexiform neurofibroma
- Sphenoid wing dysplasia; congenital bowing or thinning of long bone cortex w/wo pseudoarthrosis
- Bilateral optic nerve gliomas
- 2/more Lisch nodules on slit lamp
- First degree relative with NF1
Epidemiology

- **NF1**: 1:4000
- **NF2**: 1:50,000
- **All races**
  - Males slightly more than females
- **Autosomal dominant**
Co-Management

- Orthopedics: kyphoscoliosis and tibial bowing
- Plastics: reconstructive surgery on facial asymmetry
- Psychology: language disorders and learning disabilities
- Ophthalmology: Lisch nodules
- Neurology: Optic glioma, acoustic neuromoma, neurofibrosarcoma
- Genetic counseling
Diabetes Mellitus

- Acanthosis Nigricans
- Necrobiosis Lipoidica
- Peripheral Neuropathy
- Peripheral Vascular Disease
- Scleredema Diabeticorum

- Diabetic Dermopathy
- Diabetic Bullae
- Eruptive Xanthoma
- Infection: Furuncles, paronychia, cellulitis, dermatophytoses
- Candidiasis
Diabetic Bullae

- Large intact bullae
- Arise spontaneously on legs, feet, dorsa of hands and fingers
- Rupture→oozing bright red erosions, heal after several weeks
- Trauma or immunologic mechanism has been indicated
Acanthosis Nigricans

- Associated with insulin resistance in DM
- Brown→Black velvety hyperpigmentation
- Usually in body folds: posterior and lateral folds of the neck, axillae, groin, umbilicus
- Prominent feature of obesity, polycystic ovary syndrome, Donohue syndrome, Rabson-Mendenhall syndrome
- Medications: glucocorticoids, niacin, insulin, OCP, protease inhibitors
Necrobiosis Lipoidica

- Erythematous papules over pretibial areas
- Well-demarcated atrophic yellow→red brown
- Female:Male 3:1
- Severity not related to severity of diabetes
- Control of diabetes has no effect on course of NLD
NLD Differential Diagnosis

- Granuloma Annulare
- Morphea
- Stasis dermatitis
- Cellulitis
- Sarcoidosis, lichen sclerosis
- tertiary syphilis
- Hansen's disease
NLD Treatment

- Intrallesional steroid injections
- Tretinoin
- Topical steroids
- Laser
- Topical PUVA
- Less common: cyclosporin, excision, skin grafting
Scleredema Diabeticorum

- Onset correlates with duration of diabetes and presence of microangiopathy
- Poorly demarcated scleroderma-like induration of skin and subcutaneous tissue of upper back, neck, proximal extremities
- 2.5-14% of patients with diabetes
- Rapid onset and progression
Treatment

- PUVA
- UVA
- UVB
- Corticosteroids
- Chemotherapy, radiation
- Physiotherapy
- Tight glycemic control
Diabetic Dermopathy

- Circumscribed atrophic depressed lesions on lower legs
- Arise in crops, gradually resolve
- 4/more lesions almost always limited to patients with diabetes
- Accompanied by microangiopathy
- Asymptomatic
- No treatment necessary
Eruptive Xanthoma

- Discrete inflammatory papules
- Erupt suddenly in showers
- Buttocks, elbows, lower arms, knees
- Dome-shaped, red→yellow center with red halo
- Resolve with low-calorie low-fat diet
Pyoderma Gangrenosum

- Rapidly evolving, idiopathic, chronic
- Most commonly associated with chronic ulcerative colitis
  - Less common: arthritis, hematologic dyscrasias, malignancy; rarely occurs alone
- Irregular, boggy ulcers with undermined borders surrounding purulent necrotic bases
Epidemiology

- Rare, unknown prevalence
- All age groups, peak between 40-60 years
- Slight preponderance in females
Pathogenesis

- No microbiological etiology
- Neutrophilic dermatosis: massive neutrophilic infiltrates within the skin
Clinical Manifestation

- **Acute:** Painful hemorrhagic pustule or nodule de novo or after minimal trauma
- **Chronic:** Slow progression, less painful, with granulation and hyperkeratosis
Skin Lesions

- Acute
  - Superficial hemorrhagic pustule surrounded by erythematous halo
  - Very painful
  - Ulcer borders dusky-red, purple, irregular, boggy
  - Base is purulent, necrotic
  - Pustules at advancing border and base of lesion
  - Halo of erythema spreads centrifugally
Skin Lesions

• **Chronic**
  - Lesions slowly progress
  - Large areas of the body
  - Massive granulation within ulcer
  - Lesions usually solitary
  - Lower extremities, buttocks, abdomen
  - Healing ulcers results in thin atrophic cribiform scars
Associated Systemic Disease

- Up to 50% occur without associated disease
- Large and small bowel disease: Crohn disease, ulcerative colitis, diverticulosis, arthritis, leukemia, chronic hepatitis, Behcet syndrome
Treatment

- Treat underlying disease
  - oral/IV glucocorticoid steroids
  - Sulfasalazine
  - Sulfones
  - Cyclosporine
  - Biologics: infliximab, etanercept, adalimumab
- Topical: tacrolimus ointment, intralesional triamcinolone
Vasculitis

- Giant Cell Arteritis
- Hypersensitivity Vasculitis
- Nodular Vasculitis
- Polyarteritis Nodosa
- Urticarial Vasculitis
- Wegener Granulomatosis
Hypersensitivity Vasculitis

- Hypersensitivity to antigens from infectious agents, drugs, exogenous/endogenous
- Palpable Purpura primarily lower legs
- Lesions do not blanch
- Systemic: kidney, muscles, joints, GI tract, peripheral nerves
- All ages
- Male:Female equal
Etiology

- **Infections**
  - Hep B Hep C
  - Group A Strep
  - Staph Aureus
  - Mycobacterium leprae

- **Neoplasms**
  - CA Kidney
  - SLE
  - RA
  - Sjögren

- **Drugs**
  - Sulfonamides
  - Penicillin
  - Dysprotenemias
    - Cryoglobulinemia
    - Paraproteinemia
    - Hypergammaglobulinemia
    - congenital deficiencies of complement

  *Idiopathic*
Hypersensitivity Vasculitis Management

- Antibiotics for bacterial infection
- Prednisone for moderate/severe disease
- Immunosuppressives: Cyclophosphamide, azathioprine in combination with prednisone, Cyclosporine, IV immunoglobulin
Polyarteritis Nodososa

- Multisystem necrotizing vasculitis
- Small and Medium muscular arteries
- Involvement of renal and visceral arteries
- Mean age 45 years
- Male:Female 2.5:1
- Etiology unknown

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Polyarteritis Nodosa

- **Chronic:**
  - **Cardio:** CHF, MI, hypertension, pericarditis
  - **Neuro:** CVA, mixed motor/sensory involvement
  - **Muscles:** diffuse myalgias
  - **GI:** n/v, abd. pain, hemorrhage, infarction
  - **Eyes:** ocular vasculitis, retinal artery aneurysm, optic disc edema/atrophy
  - **Kidneys:** renal failure, edema
  - **Testes:** pain, tenderness
Polyarteritis Nodosa

- **Skin:**
  - 15% of all cases
  - Bright red→bluish nodules
    - follow course of involved arteries
    - bilateral lower legs, thighs
    - duration: days to months
    - resolve with residual violaceous PIH
  - lesions in systemic and cutaneous: identical
Polyarteritis Nodosa

- **Course and Prognosis:**
  - Untreated: high morbidity and mortality
  - Cutaneous: chronic, relapsing, benign course

- **Management:**
  - **Systemic**
    - Prednisone 1 mg/kg/day
    - Cyclophosphamide 2 mg/kg/day
  - **Cutaneous**
    - Nonsteroidal anti-inflammatory agents
    - Prednisone
Henoch-Schonlein Purpura

- Hypersensitivity vasculitis: mainly in children
- History: URI, 75% group A Strep
- Palpable purpura
- Bowel angina: abdominal pain worse after meals
- Bowel ischemia, bloody diarrhea
- Kidney: hematuria
- Artiritis
- 5% long-term morbidity, renal disease
Henoch-Schonlein Treatment

- Bed rest, supportive care
- Appropriate antibiotics
- Serial UA
- Corticosteroids debatable: helpful for short periods with GI complications or chronic glomerulonephritis
Kawasaki Disease

- 85% < 10 years
- 50% < 2 1/2 years
- Triphasic
  - Acute period
  - Subacute period
  - Convalescent period
Kawasaki Disease

- **Acute febrile period**
  - ~12 days
  - Abrupt onset of fever

- **Subacute period**
  - ~30 days
  - Resolution of fever, thrombocytosis, desquamation
  - Highest risk of sudden death

- **Convalescent period**
  - 8-10 weeks after illness
  - Signs of illness disappeared, ends when SED rate normal
  - Small number of deaths in this period
Kawasaki Disease Management

- **Most important:** diagnosis, prevention of coronary aneurysm and MI

- **Repeated echocardiogram, EKG, Lab evaluation**

- **IV gamma globulin**

- **ASA**

- **Corticosteroids contraindicated:** increase risk of coronary artery aneurysm
Kawasaki Disease Diagnosis

- **Five of Six Criteria:**
  - Fever lasting at least 5 days
  - Four of following features:
    - Changes in peripheral extremities: acute erythema and edema of hands and feet, convalescent desquamation of fingertips
    - Polymorphous exanthem
    - Bilateral painless bulbar conjunctival injection without exudate
    - Changes in lips and oral cavity (erythema, cracking lips, strawberry tongue, diffuse injection or oral and pharyngeal mucosa)
    - Acute nonpurulent cervical adenopathy, usually unilateral
Wegener Granulomatosis

Granulomatosis with Polyangitis

- Ulcers resemble pyoderma gangrenosum
- Papules, vesicles, palpable purpura
- Most common on lower extremities
- Oral ulcers, gingival hyperplasia
- Nasal mucosal ulcers, crusting, nasal septal perforation, saddle-nose deformity
Systemic Symptoms

- Fever, paranasal sinus pain, purulent or bloody nasal discharge
- Cough, hemoptysis, dyspnea, discomfort
- External auditory canal pain, OM, mild conjunctivitis, scleritis, granulomatous sclerouveitis, ciliary vessel vasculitis
- Cranial neuritis, cerebral vasculitis
- Renal failure in advanced disease 85%
Differential Diagnosis

- Other vasculitides
- Goodpasture syndrome
- Tumors of the upper airway and lung
- Infectious/noninfectious granulomatous disease (blastomycosis)
- Lymphoma
- Allergic granulomatosis
Etiology

- Any age, mean age 40
- Equal male:female ratio
- Rare in blacks
- Unknown etiology
Laboratory

- Mild anemia, Leukocytosis, ± thrombocytosis
- ESR markedly elevated
- Impaired renal function
- Proteinuria, hematuria, RC casts
- Antineutrophil cytosplasmic autoantibodies (ANCA) are seromarkers
  - Cytoplasmic pattern (c-ANCA)
  - Perinuclear pattern (p-ANCA)
  - Titers correlate with disease activity
Pathology

- *Necrotizing vasculitis of small arteries/veins, granuloma formation*
- *Kidneys: glomerulonephritis*
Imaging

- Paranasal sinuses: opacification with or without sclerosis
- Chest: pulmonary infiltrates, nodules; consolidation upper lobes
Management

- **Cyclophosphamide**: 2mg/kg/day. Dose adjusted for leukocyte 5000/µL (neutrophil count 1500/µL). Therapy 1 year after complete remission
  - Alternative: azathioprine if cyclophosphamide not tolerated
- **Presnisone**: 1 mg/kg/day x 1 month, tapered to alternate day doses x 6 months
- **Rituximab**: refractory patients
- **Trimethoprim-Sulfamethoxazole**: prevent upper airway bacterial infections; adjunctive therapy
Prognosis

- Untreated fatal due to renal failure
- Cyclophosphamide and prednisone therapy gives long-term remission in 95%
References


